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AN INTRODUCTION TO SEBACEOUS GLANDS*

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The sebaceous glands in man are aggregates of various-sized acini that empty into a duct. Glandular configuration is determined by the relative size of the glands in any given area and the number of other glands in the same area; that is, by the amount of crowding they are subjected to and by the nature of the dermis in which they grow. Regardless of differences in size, shape, or position, their cellular morphology and sequence of differentiation are similar but not necessarily identical. As the term is used in this volume, sebaceous differentiation is the orderly synthesis, segregation, and accumulation of lipid droplets which culminate in enlarged, misshapen cells that fragment to form sebum.

Sebaceous glands, particularly the very large ones, are richly supplied with blood vessels. The larger acini are compressed masses of lobular units separated by trabeculae of extremely delicate connective tissue; therefore in tissue sections, blood vessels sometimes appear to be inside the acini.

For the most part, the glands are structurally alike. Each acinus is attached to a common excretory duct (Fig. 1) composed of cornifying, stratified squamous epithelium which is continuous with the wall of the pilary canal and indirectly with the surface epidermis. Acini characteristically develop by the centripetal enlargement of the cells. Those in the center are large, misshapen, or undergoing fragmentation; those at the periphery are undifferentiated and sometimes resemble epidermal cells. Like the individual cells within each acinus, the acini within each glandular unit vary according to their state of differentiation. Occasional small acini, which appear to be completely immature, show little or no lipid accumulation in any of their cells; others have visible lipid droplets only around the nuclei in the central cells. Finally, some acini are full of lipid-laden cells that extend to the periphery of the acinus and abut against undifferentiated peripheral cells that are so greatly attenuated that they sometimes escape observation. The life cycle of sebaceous cells culminates in the accumulation of so much lipid in their cytoplasm that they eventually die and fragment. The centers of mature acini and the ducts contain a melange of lipids, cellular detritus, flakes of keratinized cells, and microorganisms. Although differentiating sebaceous cells have some tonofilaments that are identical with those in epidermal cells, they are characterized by bimodal differentiating potentialities. Bimodality is especially evident in the cells of the ducts, which are normally lined with stratified squamous epithelium whose superficial keratinized cells often contain lipid droplets.

With some exceptions, other mammals besides man have numerous sebaceous glands only in the external auditory meatus and around the facial area and perineum. The abundant fields of glands in the ears of rabbits and in the costovertebral spot (flank organ) of hamsters, and a number of other examples, react so readily to steroid hormones that they warrant some mention later on in this symposium. Some mammals are relatively free of sebaceous glands, and whales and porpoises apparently lack them altogether. Of the many mammals studied, only lemurs have glands that are about as numerous and large as they are in man.

In most animals, including man, the sebaceous glands are appendages of hair follicles and open inside the pilary canals (Fig. 2). In adult lemurs, however, the long, tortuous ducts of these glands open directly onto the surface of the hairy skin (Montagna and Yun, 1962); originating from hair follicles, they become separated in the first postnatal month (Yun and Montagna, 1964). In some animals, large aggregates of glands, such as the preputial and inguinal glands in rats, mice, rabbits, and gerbils, are held together by tough connective tissue. Marmosets, tamarins, and shrews have large fields of abdominal sebaceous glands and tarsiers have huge labial glands. The meibomian glands in the palpebrae appear to be specialized glands.

Since most sebaceous glands arise from hair follicles, they appear in cephalocaudal sequence. Three-and-a-half-month-old fetuses have well-formed glands in the scalp and face, where hair follicles differentiate first, but none elsewhere on the body (Serri and Huber, 1963). Even before the embryonic hair follicles become slanted or begin to form a hair, they develop two humps on the outer root sheath, one above the other. The lower is the "bulge" proper, to which the fibers of the arrectores pilorum muscles will later attach; the upper is the anlage of a sebaceous gland. When the follicles become slanted, the bulges are oriented on the follicle margin facing the obtuse angle with the surface epidermis.

The cells in these sebaceous anlagen are identical with those in the basal layer of the epidermis and of the pilary canal. Primordial sebaceous cells have a high nucleocytoplasmic ratio; hence the cytoplasm stains well with most basic dyes. Since this basophilia is abolished by crystalline ribonuclease, it is probably RNA. Seen under the electron microscope, the cytoplasm of these cells contains numerous aggregates of glycogen, tonofilaments, a high concentration of free ribosomes, a few profiles of granular rough endoplasmic reticulum (RER)

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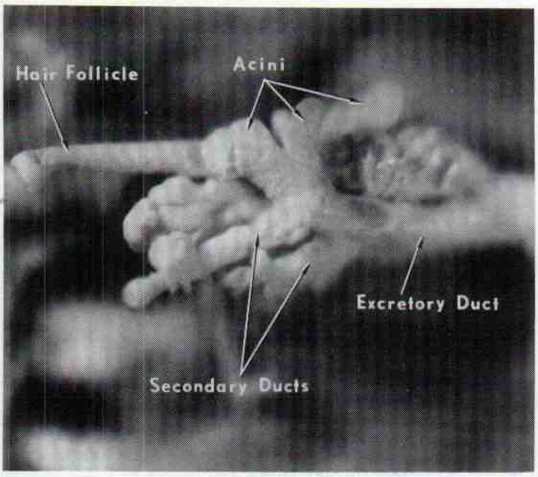

FIG. 1: Intact sebaceous gland from a split-skin preparation showing the acini converging toward the major excretory duct.

FIG. 2: Intact sebaceous glands from the scalp still attached to their respective hair follicles. From the split skin of the scalp.

and agranular smooth endoplasmic reticulum (SER), and small Golgi zones. The apposing membranes of adjacent cells are attached by desmosomes, and the basal cells have hemidesmosomes against the basal lamina (Bell, this issue).

By the fourth month of gestation, most of the glands on the head are nearly mature; they appear elsewhere on the body at various times after the hair follicles are formed. When the large mature cells in the center of the primordial glands are fully extended and misshapen, their cell membranes rupture. A similar kind of differentiation also occurs in the cells in the center of the future duct, which at first is a solid cord. Duct cells differentiate linearly in a column that extends through the epidermis to the surface and proceeds for a distance parallel to it. When filled with vesicles of sebum, these cells lose their integrity, rupture, and form a channel that establishes the first pilosebaceous canal. Fetal sebaceous glands are large, more so in males than in females, are apparently functional, and no doubt contribute to the vernix caseosa. The glands are also large in newborn infants; regressing shortly after birth, they remain relatively small in infancy and most of childhood and develop again in prepuberty. The small glands of prepubertal children share some of the features of fetal anlagen, e.g., high concentrations of free ribosomes, tonofilaments, large Golgi zones, and some profiles of SER.

In the labia minora of infant girls, where hair follicles develop and later mostly disappear (Erickson and Montagna, 1972), the sebaceous glands consist of nests of lobules sometimes arranged around a minute vellus hair follicle (Fig. 3). Small, disoriented hair follicles are sometimes found in the labial sebaceous glands of mature women. Miles (1963) found one hair follicle with the sebaceous glands in the buccal mucosa.

Most adult human beings normally have sebaceous glands on the buccal, oral, and even gingival mucosa (Fordyce spots (Miles, 1958a,b; 1963). After adolescence they also develop in the glabrous vermilion border of the lips, more numerous in the upper than in the lower lip, where they develop without hair follicles.

Appearing at puberty, sebaceous glands in the

FIG. 3: Nests of large sebaceous glands free of hair follicles from a labium minus of a woman 23 years old. Split-skin preparation.

mucous membranes continue to increase in number particularly after the age of 35. They probably differentiate directly from the epithelium of the lips and of the buccal and oral cavities. Histologic studies of these areas in subadolescents show no sebaceous gland anlagen.

Sebaceous differentiation also occurs in other organs: in the parotid and submaxillary glands of men and women (Hartz, 1946; Andrew, 1952; Meza Chavez, 1949), the cervix uteri (Nicholson, 1918–1919; Dougherty, 1948; Donnelly and Navidi, 1950), between the lactiferous ducts at the tip of the nipple of mammary glands in men and women (Montagna, 1970), in the tubercles of Montgomery (Montagna and Yun, 1972), and in the epithelium of the larynx (Geipel, 1949) and esophagus (de La Pava and Pickren, 1962).

Much will be written subsequently in this volume about the structure and cell differentiation of sebaceous glands. A brief sketch of some cytologic details will suffice here.

Viewed under the light microscope, sebaceous cells appear to differentiate first in the center, where perinuclear vesicles gradually accumulate and eventually fill the cytoplasm; once lipid accumulation is complete, the cytoplasm is reduced to flimsy, intervesicular strands. As individual cells accumulate lipid droplets, they attain many times their former volume and cause the entire glandular fundus to enlarge (see Tosti, this issue). Round and relatively intact, the nucleus remains about the same size until the later stages of cell disintegration when it shrinks and disappears.

Although numerous authors have studied sebaceous glands in man and other mammals, apparently only Montagna and his colleagues have found active melanocytes in them. What role they play, in the glands or elsewhere, is still unknown. Active melanocytes were first seen in the sebaceous glands of the Atlantic seal (Montagna and Harrison, 1957), later in the glands of lemurs and other primates (Montagna et al., 1961; Montagna, 1962; Montagna and Yun, 1962). They are numerous in the sebaceous glands of the eyebrows and in the glands of Zeiss (Montagna and Ford, 1969; Montagna, 1970) where mature sebaceous cells usually contain some melanin granules. Most recently, active melanocytes have been found in the large sebaceous glands of the nipples and areolae of women's breasts (Montagna, 1970; Montagna and Yun, 1972), with long dendrites extending for some distance between differentiating cells. In black lemurs, melanin is so copious that even the sebum is dark brown.

Once mature sebaceous cells die and form sebum, they are replaced by dividing undifferentiated cells which balance the loss. How this is accomplished is still debatable. Bizzozero and Vassale (1887), Stamm (1914), Kyrle (1966), Schaffer (1927), and Epstein and Epstein (1966) all considered the cells at the periphery of the acini as the source of mitotic activity. Other authors (Bab, 1904; Brinkmann, 1912; Clara, 1929) felt that mitosis occurred mainly in the epithelium of the ducts at their junction with the acini. Despite their differences, all of these authors agreed that new cells migrate toward the center of the glands. Arguing for the dynamics of growth solely on the location of mitotic activity is a trifle foolhardy. In concentrating on the foci of mitotic activity, most investigators have failed to explore what is probably a more important feature of growth, the shape of the glands. If their complex shape is ignored, arguments about the origin of mitotic activity that are based solely on the locus of that activity can yield only faulty or uninterpretable data. Epstein and Epstein (1966), who studied mitosis in scalp and arm skin injected with thymidine-^{3}H, partially avoided this pitfall (see Weinstein, this issue).

The shape and size of sebaceous glands can best be appreciated in split-skin preparations where their nearly intact relationship with epidermis and hair follicles is maintained and where the findings from histologic preparations are further confirmed. The gross appearance and histology of sebaceous glands are affected by their size, the amount of crowding of the acini, and the various stages of maturity. In uncrowded areas where the glands are usually small to medium sized, a few rounded or sacculated acini clearly converge toward a duct more or less in the center of the aggregate. In large, normally crowded or compressed, distorted glands, however, many of the acini are separated by barely visible, very delicate connective tissue septa. These discrete, intact glands resemble heads of cauliflower. In them, undifferentiated cells are squeezed between the sometimes fused adjacent acini, or, for that matter, almost anywhere in the glandular mass, whereas in undistorted glands they appear mostly at the periphery of the individual acini. Hence the location of mitotic cells in neatly defined glandular acini differs from that in deformed ones. Sebaceous differentiation can and does occur wherever undifferentiated potential sebaceous cells are present, whether at the periphery of an acinus or elsewhere. Furthermore, the epithelial buds that grow from the walls of the ducts differentiate, grow into sebaceous acini, expand, and, in a crowded environment, encroach upon nearby acini, sometimes fusing with them and becoming part of larger units. The boundaries of fused acini are discernible in the small, elongated, undifferentiated sebaceous cells and the traces of connective tissue and fibrocytes that adhere to them. Such trabeculae sometimes extend into or across the body of large and medium-sized sebaceous units. Sebaceous acini can also develop from the undifferentiated cells at the periphery of existing acini.

In any consideration of glandular growth, it must be remembered that although the glands are often obliterated in acne lesions and other pathologic conditions (Knutson, this issue), apparently the ductal tree remains undamaged. Thus, when the lesion heals, the gland regrows, probably from ductal cells. Moreover, glands easily regenerate from the cells of the outer root sheath of hair follicles after they have been destroyed by dermabrasion (Strauss and Kligman, 1958; Staricco, 1960). According to Epstein and Epstein (1966), the steady-state replenishment from the periphery of the acini is from two to four weeks and the average renewal time is about seven and one-half days (see Weinstein, this issue).

Even epidermal cells undergo sebaceous transformation when unduly irritated. Eisen et al. (1955) studied shallow wounds that had destroyed the proximal portion of pilosebaceous systems together with the surrounding epidermis. During the reparative process, after an initial burst of mitosis in the basal cells of pilary canals and in the remaining basal undifferentiated glandular and ductal cells, the cells flowed to the surface of the wound where they differentiated mostly into keratinocytes; some, however, underwent sebaceous transformation on the surface.

Finally, Bullough and Laurence (1970) found a water-soluble substance in skin which can be precipitated by ethanol and activated by adrenalin and hydrocortisone and which inhibits mitotic activity in sebaceous glands in vitro and in vivo. This substance is believed to be a sebaceous gland chalone (see Weinstein, this issue).

Like all introductions, this one was intended to lead the reader into the volume itself. The contributions found herein will supply all the known details about the normal and abnormal biology of these organs.

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